REMARKS

Claims 1-68, 81, 87, and 89 remain pending in this application. Claims 5, 8, 10, 11, 15-21, 23, 24, 26, 29, 31, 33-35, 41, 42, 64, 66, 67, 81 and 89 have been amended without prejudice.

A. Obvious-Type Double Patenting Rejection

The Examiner has issued a rejection under the judicially created doctrine of obviousness-type double patenting of claims 1-68, 81, 87, and 89 as being unpatentable over claims 1-38 of U.S. Patent No. 6,248,345 (hereinafter "the '345 patent"). Applicants believe the claimed invention is patentable over the '345 patent, as explained below.

B. Rejection under 35 U.S.C. § 112, first paragraph

In the Office Action, the Examiner objected to the specification under 35 U.S.C. § 112, first paragraph, asserting that "[t]he instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation." The Examiner specifically asserted, '[a]pplicant fails to set forth the criteria that defines those procedures useful for determining either the mean C_{max} "measured by microdialysis in the tissue at the site" in-vivo, or the T_{max} of bupivacaine "at the tissue site" in-vivo to practice the instant invention as herein envisioned. Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain these medicament levels without undue experimentation. In the instant case, only a limited number of examples for those procedures useful for determining either the mean C_{max} . . . or the T_{max} . . . to practice the instant invention . . . thereby failing to provide sufficient working examples." The Examiner specifically cited "*In re Wands*, 8 U.S.P.Q. 2d 1400 (CAFC 1988) at 1404", where the Court enumerated eight factors to consider when determining whether a disclosure meets the enablement requirement under 35 U.S.C. § 112.

The Examiner rejected claims 33-68 and 81, under 35 U.S.C. § 112, first paragraph, for the same reasons set forth above with respect to the objection to the specification.

The objection and rejection are respectfully traversed.

The law is clear that Applicants are not required to exemplify every procedure for determining C_{max} and T_{max} which would be encompassed by the claims. In *United States v. Telectronics, Inc.*, for example, the U.S. Court of Appeals for the Federal Circuit found that "[s]ince one embodiment is admittedly disclosed in the specification, along with the general manner in which its current range was ascertained, we are convinced that other permutations of the invention could be practiced by those skilled in the art without undue experimentation." 8 U.S.P.Q. 2d 1217, 1223 (Fed. Cir.1988), *cert. denied*, 490 U.S. 8 U.S.P.Q. 2d 1046 (1989) (citing *SRI Int'l v. Matsushita Elec. Corp. of America*, 775 F.2d 1107, 1121, 227 U.S.P.Q. 577, 586 (Fed. Cir. 1985) (the law does not require an applicant to describe in his specification every conceivable embodiment of the invention)).

Further, "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." MPEP 2164.01(b) (8th Edition), Revision 2 (citing *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 84 (C.C.P.A. 1970). *See also, Spectra-Physics, Inc. v. Coherent, Inc.* (827 F.2d 1524, Fed. Cir. 1987) "Nonenablement is the failure to disclose *any* mode, and does not depend on the applicant advocating a particular embodiment or method for making the invention."*Id.* at 1533-34.

The present specification describes in great detail the methodology of microdialysis used in determining the C_{max} or T_{max} of the formulations of the presently claimed application. Indeed, Example J at page 247 of the specification is directed to a "microdialysis study". Further, as

acknowledged by the Examiner, a number of examples to determine mean C_{max} and T_{max} using the microdialysis method are detailed in the present application. The specification at page 49 also incorporates by reference and discusses, MICRODIALYSIS IN THE NEUROSCIENCES, Techniques, volume 7, Chapter 1, pages 1-64, which reviews methods of microdialysis. One of skill in the art, in view of the specification would easily understand how to use microdialysis in the present application to determine C_{max} and T_{max}.

Furthermore, it is well recognized that "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *Telectronics* at 1223. "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art." *In re Wands*, 8 U.S.P.Q. 2d at 1404 *(citations omitted)*. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.* (Emphasis added). It is also worth noting that "it is not necessary that a court review all the *Wands* factors to find a disclosure enabling. They are illustrative, not mandatory." (Emphasis added) *Amgen, Inc. v. Chugai Pharmaceutical Co., LTD.*, 927 F.2d 1200,1213 (Fed. Cir.1991).

By its very nature, the formulation of pharmaceuticals requires clinical (i.e., *in vivo*) evaluation, and those of skill in the art are well versed in the procedures needed to ascertain C_{max} and T_{max}. For a drug formulator of ordinary skill in the art, evaluation of blood plasma data is routine. Applicants respectfully submit that the specification clearly meets the enablement requirement.

Moreover, microdialysis is such a common and widely known method that even a simple search on the internet search engine, "Google", using the term "microdialysis", retrieves 58,100

results. Among the results are a plethora of books and other publications devoted to detailed reviews/analyses of microdialysis. Clearly, microdialysis is not only commonly known among those of skill in the art, but is also easily accessible and can be understood even by laymen.

Therefore, Applicants respectfully request that the objection to the specification and rejection of independent claims 33, 35 and 81 be withdrawn. As claims 34, 37-40 and 43-68 depend from and incorporate the limitations of claim 33, they too are clear and fully supported by the specification, and the rejection should be withdrawn. As claims 41 and 42 depend from and incorporate the limitations of claim 35, they too are clear and fully supported by the specification and the rejection should be withdrawn.

In the Office Action, the Examiner objected to the specification under 35 U.S.C. § 112, first paragraph, specifically asserting that "[a]pplicant fails to set forth the criteria that allows the skilled artisan to evaluate those therapeutic benefits herein envisioned by the instant 'USP paddle method', or the 'von Frey hair' absent undue experimentation. To practice the invention as envisioned, the skilled artisan must evaluate all formulations . . . Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain these medicament levels in-vivo, as dictated by the instant claims, without undue experimentation."(Emphasis added)

The Examiner rejected claims 10-11, 15-18, 20-21, 24, 26-31, 45-46 and 48-49 under 35 U.S.C. § 112, first paragraph, for the same reasons set forth above with respect to the objection to the specification.

With respect to claims 16, 17, 20-21, 24, 26-31, 45-46 and 48-49 (and all the claims they depend from), there is no mention of the USP Paddle Method or the von Frey hair method in the claims . Applicants respectfully request clarification on this point. Otherwise, it is respectfully submitted that this rejection be withdrawn.

With respect to claims 10, 11, 15 and 18, the law does not require an applicant to describe every conceivable embodiment of the invention. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation . . . Since one embodiment is admittedly disclosed in the specification, along with the general manner in which its current range was ascertained, we are convinced that other permutations of the invention could be practiced by those skilled in the art without undue experimentation." *Telectronics,* 8 U.S.P.Q. 2d at 1223.

Moreover, it is clear that "[the test of enablement] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands* at 1404.

Applicants respectfully submit that both the USP Paddle Method and the von Frey hair methods are well known in the pharmaceutical field and those of ordinary skill in the art would easily be able to ascertain how to test a given formulation utilizing either of these methods. The Examiner's attention is respectfully directed to U.S. Patent Nos. 4,844,910 and 4,803,080, which (like the present application) recite the USP Paddle Method in the claims as well as in the specifications, without any further explanation of the method. Clearly, the USP Paddle Method is well known in the art. In addition, Applicants respectfully submit that it would be unduly burdensome to test every conceivable formulation covered by the claims of the present application.

In view of the above, it is respectfully requested that the rejections be withdrawn.

C. Rejection Under 35 U.S.C. § 112, second paragraph

In the Office Action, the Examiner rejected claims 33-68 and 81 under 35 U.S.C. § 112, second paragraph, asserting that the claims are indefinite "for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Specifically, the Examiner asserted that the phrases, "measured by microdialysis in the tissue at the site", and "at the tissue site" render the claims indefinite.

The Examiner's attention is respectfully directed to page 247 of the present specification, wherein the Applicants in great detail describe how to measure tissue concentrations using the microdialysis method, going through the procedure step-by-step. One of ordinary skill in the art would easily understand both the meaning of the phrases "measured by microdialysis in the tissue at the site" and "at the tissue site" as well as how to measure pharmacokinetic parameters at the tissue site where the microspheres are administered in the presently claimed application. Therefore, Applicants respectfully submit that independent claims 33, 35 and 81 are clear and fully supported by the specification and the rejection should be withdrawn. As claims 34, 37-40 and 43-68 depend from and incorporate the limitations of claim 33, they too are clear and fully supported by the specification and this rejection should be withdrawn. As claims 41 and 42 depend from and incorporate the limitations of claim 35, they too are clear and fully supported by the specification and the rejection should be withdrawn.

In the Office Action, the Examiner rejected claims 50-54 under 35 U.S.C. § 112, second paragraph, asserting that the claims are indefinite "for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Specifically, the Examiner asserted that the phrase, "mean somesthetic response" renders the claims indefinite as "[e]xamples of what a 'mean somesthetic response' would be are not set forth in the specification."

In response, the Examiner's attention is respectfully directed to the specification at page 164, which explains that analgesia and anesthesia achieved in a patient can be measured by the patient's response to somesthetic testing, which is defined as temperature perception. The definition of the term "mean" is well known even by laymen and is clearly defined in the specification at page 8 as "the arithmetic mean value measured across a human population". The specification provides a Table at page 164 illustrating the somesthetic test results versus time for administration of EDLA or IDLA formulations or aqueous bupivacaine. From this, it is evident that the phrase "mean somesthetic response", as recited in claims 50-54, is clearly supported by the specification. Therefore the claims are indeed clear and definite and the rejection should be withdrawn.

In the Office Action, the Examiner rejected claims 1-32, 87 and 89 under 35 U.S.C. § 112, second paragraph, asserting that "[a] broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite. . ." The Examiner further asserted that "claims 1 and 89 recite the broad recitations of 65:35DL copolymer of lactic and glycolic acid, and 60% to 85% bupivacaine free base, and the claims also recite copolymer having a molecular weight of about 40,000 Daltons to 120,000 Daltons and 'bupivacaine free base from about 45 mg to about 360 mg', which the Examiner asserts is a narrower statement of the range/limitation."

In response, Applicants respectfully submit that this rejection of claims 1-32, 87 and 89 is based on an incorrect interpretation of the claim language. Independent claims 1 and 89 recite as follows:

Claim 1. A method for providing local analgesia, local anesthesia or nerve blockade in a human, comprising administering at a site in a human a formulation comprising a plurality of controlled release microspheres comprising bupivacaine free base and a biocompatible, **biodegradable polymer comprising a 65:35 DL copolymer of lactic and glycolic acid** having free

carboxylic acid end groups, said **copolymer having a molecular weight of about 40 kDa to about 120kDa**, said **microspheres comprising from about 60% to about 85% bupivacaine free base, by weight**, said microspheres being contained in a pharmaceutically acceptable medium for parenteral administration, said formulation having a **concentration of bupivacaine free base from about 2.25 mg/ml to about 36.0 mg/ml** and the formulation including a **total amount of bupivacaine free base from about 45 mg to about 360 mg** prior to administration, such that said formulation provides local analgesia, local anesthesia or nerve blockade at the site of administration less than about 2 hours after first administration, and a duration of local analgesia, local anesthesia or nerve blockade which lasts for at least about 1 day after first administration (emphasis added).

Claim 89. A method for providing local analgesia, local anesthesia or nerve blockade in a human, comprising administering at a site in the human a formulation comprising a plurality of controlled release microspheres comprising bupivacaine free base and a biocompatible, **biodegradable polymer comprising a 65:35 DL copolymer of lactic and glycolic acid having free carboxylic acid end groups, said copolymer having a molecular weight of about 40 kDa to about 120 kDa, said microspheres comprising from about 60% to about 85% bupivacaine free base, by weight**, said microspheres being contained in a pharmaceutically acceptable medium for administration, said formulation having a **concentration of bupivacaine free base from about 2.25 mg/ml to about 36.0 mg/ml and the formulation including a total amount of bupivacaine free base from about 45 mg to about 360 mg prior to administration**, such that said formulation provides local analgesia, local anesthesia or nerve blockade at the site of administration less than about 2 hours after first administration, and a duration of local analgesia, local anesthesia or nerve blockade which lasts for at least about 1 day after first administration (emphasis added).

Claims 1 and 89 clearly recite a formulation which comprises a plurality of controlled release microspheres and includes a total amount of bupivacaine free base from about 45 mg to about 360 mg. These microspheres comprise bupivacaine free base in an amount from about 60% to about 85% by weight and a biocompatible, biodegradable polymer. The polymer comprises a 65:35 DL

copolymer of lactic and glycolic acid. The copolymer has a molecular weight of about 40kDa to about 120kDa in a ratio of 65:35 DL.

According to the MPEP 2173.05 (c), eighth edition, Revision 2, "[e]xamples of claim language which have been held to be indefinite are (A) "a temperature of between 45 and 78 degrees Celsius, preferably between 50 and 60 degrees Celsius". In contrast, neither claim 1 nor claim 89 contains a "broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation".

Therefore, Applicants respectfully submit that claims 1 and 89 are clear under 35 U.S.C. § 112, second paragraph, and this rejection should be withdrawn. As claims 2-32, and 87 depend from and incorporate the limitations of claim 1, they too are clear and the rejection should be withdrawn.

D. Rejection Under 35 U.S.C. § 102(a)

In the Office Action, the Examiner rejected claims 33-68 under 35 U.S.C. § 102(a), asserting that the claims are anticipated by Berde *et al.* (U.S. Patent 6,046,187 or U.S. Patent No. 5,922,340). The Examiner specifically asserted, "[a]pplicants' attention is directed to *Ex parte Novitski*, 26 U.S.P.Q. 2d 1389 (B.O.P.A. 19933) illustrating anticipation resulting from inherent use, absent a *haec verba* recitation for such utility. In the instant application, as in *Ex parte Novitski*, supra, the claims are directed to preventing a malady or disease with old and well known compounds or compositions. It is now well settled law that administering compounds inherently possessing a protective utility anticipates claims directed to such protective use."

This rejection is respectfully traversed. With respect to the doctrine of inherency, "the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." MPEP, 8th edition, Revision 2, section 2112, citing *In re Rijckaert*, 9 F.3d 1531, 1534, 28 U.S.P.Q. 2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be recognized by one of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 U.S.P.Q. 2d 1949, 1950-51 (Fed. Cir. 1999).

Further, "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the alleged inherent characteristic necessarily flows from the teachings of the applied prior art." MPEP, 8th edition, Revision No. 2, section 2112, citing *Ex parte Levy*, 17 U.S.P.Q. 2d 1461, 1464 (Bd. Pat. App. And Inter. 1990) (emphasis in original).

The Examiner's attention is directed to independent claims 33 and 35, which read in pertinent part, respectively, as follows:

Claim 33. A method for providing local analgesia local anesthesia or nerve blockade **in a human** comprising **administering at a site in a human** a unit dose of microspheres comprising . . . bupivacaine free base or a pharmaceutically acceptable salt thereof, effective to provide local analgesia, local anesthesia or nerve blockade at the site of administration in the human which occurs less than about 2 hours after first administration, and a duration of local analgesia, local anesthesia or nerve blockade which lasts for at least about 1 day after

first administration, wherein the mean **Cmax of bupivacaine** measured by microdialysis in the tissue at the site is **from about 35,000 ng/ml to below a toxic concentration at the site** and wherein **the level of bupivacaine at the site of administration is at least 150 times the level of said bupivacaine in the blood plasma** (emphasis added).

Claim 35. A method for providing local analgesia, local anesthesia or nerve blockade **in a human,** comprising administering a unit dose of microspheres comprising a biocompatible, biodegradable carrier and bupivacaine or a pharmaceutically acceptable salt thereof, effective to provide **local analgesia, local anesthesia or nerve blockade at a site of administration in a human, which local analgesia, local anesthesia or nerve blockade occurs less than about 2 hours after first administration, and a duration of local analgesia, local anesthesia or nerve blockade** which lasts for at least about 1 day after first administration, **wherein the mean Tmax of bupivacaine at the tissue site occurs at a time point from about 10 hours to about 45 hours after first administration** (emphasis added).

Both claims 33 and 35 are directed to the provision of local analgesia, local anesthesia or nerve blockade in a human. In contrast, the only in-vivo data reported in the '187 and '340 patents is for animals. (See the '187 patent, Example 1 and the '340 patent, Example 1). As neither the '187 nor '340 Berde patents provide Cmax or Tmax data for administration of the disclosed formulations to a human being, it cannot be assumed that the formulations of either the '187 or the '340 patents could achieve in a human, the Cmax, Tmax, onset of local analgesia, local anesthesia, nerve blockade, level of local anesthetic at the site of administration, or the duration of action set forth in independent claims 33 and 35.

Further, even with regard to administration to animals, neither the '187 nor the '340 Berde patents teach a "Cmax of bupivacaine measured by microdialysis in the tissue at the site [is] from about 35,000 ng/ml to below a toxic concentration at the site and wherein the level of bupivacaine at the site of administration is at least 150 times the level of bupivacaine in the blood plasma" as recited in independent claim 33 nor teach "local analgesia, local anesthesia or nerve blockade at a site

of administration . . . occurs less than about 2 hours after first administration . . . wherein the mean Tmax of bupivacaine at the tissue at the site occurs at a time point from about 10 hours to about 45 hours after first administration" as recited in independent claim 35.

The formulations described in the '187 and/or '340 patents would not necessarily possess the same pharmacokinetic characteristics or parameters in humans as recited in claims 33 and 35 of the present application. Therefore, inherency has not been established.

Applicants respectfully request that the rejection be removed.

As claims 34 and 36-68 depend from and incorporate the limitations of claims 33 and 35, they also are not anticipated under section 102(a) and the rejection of these claims should be withdrawn.

E. Rejection Under 35 U.S.C. § 102(e)

In the Office Action, the Examiner rejected claims 1-68, 81 and 89 under 35 U.S.C. § 102(e), asserting that the claims are anticipated by Goldenheim *et al.* (U.S. Patent 6,451,335 or U.S. Patent No. 6,248,345).

In response, Applicants respectfully direct the Examiner's attention to independent claims 1, 33, 35, 81 and 89. Claims 33 and 35 are presented in the preceding section. Claims 1, 81 and 89 read as follows:

Claim 1. A method for providing local analgesia local anesthesia or nerve blockade **in a human**, comprising **administering at a site in a human** a formulation comprising . . . such that said formulation **provides local analgesia, local**

anesthesia or nerve blockade at the site of administration less than about 2 hours after first administration (emphasis added).

Claim 81. A method for providing local analgesia, local anesthesia or nerve blockade **in a human,** comprising **administering at a site in a human** a unit dose of microspheres comprising a biocompatible, biodegradable carrier and a local anesthetic, effective to provide local analgesia, local anesthesia or nerve blockade **at the site of administration in the human** which local analgesia, local anesthesia or nerve blockade **occurs less than about 2 hours after first administration**, and a duration of local analgesia, local anesthesia or nerve blockade which lasts for at least about 1 day after first administration, **wherein the mean Cmax of local anesthetic measured by microdialysis in the tissue at the site is from a Cmax therapeutically equivalent to 35,000 ng/ml bupivacaine to below a toxic concentration at the site** (emphasis added).

Claim 89. A method for providing local analgesia, local anesthesia or nerve blockade **in a human,** comprising **administering at a site in the human a** formulation comprising a plurality of controlled release microspheres comprising bupivacaine free base . . . . such that **said formulation provides local analgesia, local anesthesia or nerve blockade at the site of administration less than about 2 hours after first administration**, and a duration of local analgesia, local anesthesia or nerve blockade which lasts for at least about 1 day after first administration (emphasis added).

Independent claims 1, 33, 35, 81 and 89 are all directed to the provision of local analgesia, local anesthesia or nerve blockade in a human. In contrast, the only in-vivo data reported in the Goldenheim '335 and '345 patents is for animals. As neither the '335 nor '345 Goldenheim patents provide Cmax or Tmax data for administration of the disclosed formulations to a human, it cannot be assumed that the formulations of either the '335 or the '345 patents could achieve in a human, the Cmax, Tmax, onset of local analgesia, local anesthesia, nerve blockade, level of local anesthetic at the site of administration, or the duration of action recited in the rejected claims.

Further, even with regard to the administration to animals, neither the '335 nor '345 Goldenheim patents teach "the level of bupivacaine at the site of administration [is] at least 150 times the level of bupivacaine in the blood plasma" as recited in independent claim 33 nor do they teach "wherein the mean Tmax of bupivacaine at the tissue site occurs at a time point from about 10 hours to about 45 hours after first administration" as recited in independent claim 35.

As discussed above for the Berde patents, "the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." MPEP, 8th edition, Revision 2, section 2112, (citation omitted) (see discussion above). Further, "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the alleged inherent characteristic necessarily flows from the teachings of the applied prior art. MPEP, 8th edition, Revision No. 2, section 2112 (citation omitted) (see discussion above).

The formulations described in the '335 and /or '345 patents would not necessarily possess the same pharmacokinetic characteristics or parameters in humans as recited in the claims of the present application. Therefore, inherency has not been established.

Applicants respectfully request that this rejection be withdrawn.

As claims 2-32, 34 and 36-68 depend from and incorporate the limitations of claims 1, 33 and 35, they also are not anticipated under section 102 for inherency and the rejection should be withdrawn.

F. Rejection Under 35 U.S.C. § 103(a)

In the Office Action, the Examiner rejected claims 1-68, 81, 87 and 89 under 35 U.S.C. § 103(a), asserting that the claims are obvious over Goldenheim *et al.* (U.S. Patent 6,451,335 or U.S. Patent No. 6,248,345). The Examiner cited the Court of Customs and Patent Appeals, stating, "is elementary that the mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not cause a claim drawn to those things to distinguish over the prior art."

As discussed above, the doctrine of inherency requires more than "the mere fact that a certain result or characteristic may occur or be present in the prior art". MPEP, 8th edition, Revision 2, section 2112, citing *In re Rijckaert*, 9 F.3d 1531, 1534, 28 U.S.P.Q. 2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981).

As also discussed above, independent claims 1, 33, 35, 81 and 89 are all directed to the provision of local analgesia, local anesthesia or nerve blockade in a human. In contrast, the only in-vivo data reported in the Goldenheim '335 and '345 patents is for animals. As neither the '335 nor '345 Goldenheim patents provide Cmax or Tmax data for administration of the disclosed formulations to a human being, it cannot be assumed that the formulations of either the '335 or the '345 patents could achieve in a human, the Cmax, Tmax, onset of local analgesia, local anesthesia, nerve blockade, level of local anesthetic at the site of administration, or the duration of action recited in the rejected claims.

Further, even with regard to the administration to animals, neither the '335 nor '345 Goldenheim patents teach "the level of bupivacaine at the site of administration [is] at least 150 times the level of bupivacaine in the blood plasma" as recited in independent claim 33 nor do they teach "wherein the mean Tmax of bupivacaine at the tissue site occurs at a time point from about 10 hours to about 45 hours after first administration" as recited in independent claim 35.

The formulations described in the '335 and/or '345 patents would not necessarily possess the same pharmacokinetic characteristics or parameters in humans as recited in the claims of the present application.

It is respectfully requested that the rejection be withdrawn.

As claims 2-32, 34, 36-68 and 87 depend from and incorporate the limitations of claims 1, 33 and 35, they also are not obvious under § 103(a) and the rejection should be withdrawn.

G. Rejection Under 35 U.S.C. § 103(a)

In the Office Action, the Examiner rejected claims 1-68, 81, 87 and 89 under 35 U.S.C. § 103(a), asserting that the claims are obvious over Berde *et al.* (U.S. Patent 6,046,187 and U.S. Patent No. 5,922,340). The Examiner specifically asserted that claims 12-14, 19, 22-24 and 26-31, "specifically requires administration of injectable pharmaceutical compositions. Berde *et al.* employed the claimed compound in dermal form and injectable form, not specifically reciting another formulation."

As discussed above, the doctrine of inherency requires more than "the mere fact that a certain result or characteristic may occur or be present in the prior art". MPEP, 8th edition, Revision 2, section 2112, citing *In re Rijckaert*, 9 F.3d 1531, 1534, 28 U.S.P.Q. 2d 1955, 1957 (Fed. Cir. 1993)

(reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981).

As also discussed above, independent claims 1, 33, 35, 81 and 89 are all directed to the provision of local analgesia, local anesthesia or nerve blockade in a human. In contrast, the only in-vivo data reported in the Berde '187 and '340 patents is for animals. As neither the '187 nor '340 Berde patents provide Cmax or Tmax data for administration of the disclosed formulations to a human being, it cannot be assumed that the formulations of either the '187 or the '340 patents could achieve in a human, the Cmax, Tmax, onset of local analgesia, local anesthesia, nerve blockade, level of local anesthetic at the site of administration, or the duration of action recited in the rejected claims.

Further, even with regard to the administration to animals, neither the '187 nor '340 Berde patents teach a "Cmax of bupivacaine measured by microdialysis in the tissue at the site [is] from about 35,000 ng/ml to below a toxic concentration at the site and wherein the level of bupivacaine at the site of administration is at least 150 times the level of bupivacaine in the blood plasma" as recited in independent claim 33 nor teach "local analgesia, local anesthesia or nerve blockade at a site of administration . . . occurs less than about 2 hours after first administration . . . wherein the mean Tmax of bupivacaine at the tissue site occurs at a time point from about 10 hours to about 45 hours after first administration" as recited in independent claim 35.

The formulations described in the '187 and/or '340 patents would not necessarily possess the same pharmacokinetic characteristics or parameters in humans as recited in the claims of the present application. It is respectfully requested that the rejection be withdrawn.

As claims 2-32, 34, 36-68 and 87 depend from and incorporate the limitations of claims 1, 33 and 35, they also are not obvious under § 103(a) and the rejection should be withdrawn.

CONCLUSION

It is now believed that the above-referenced rejections have been obviated and it is respectfully requested that the rejections be withdrawn.

According to currently recommended Patent Office policy the Examiner is specifically authorized to contact the undersigned in the event that a telephonic interview will advance the prosecution of this application.

An early and favorable action is earnestly solicited.

Respectfully submitted,
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